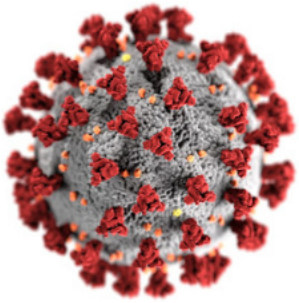


COVID-19 Action Newsletter

UT Southwestern Department of Internal Medicine
James Luby, M.D., and Robert Haley, M.D., editors

The Situation: India at the Epicenter—Confirmed Cases There > 350,000 per day

In the world as of April 26, 2021, 147,325,436 cases and 3,112,206 deaths have been confirmed. In the United States, there have been 32,088,686 confirmed cases, the most in the world followed in order by India, Brazil, Russia and the United Kingdom. China is now 91st in the world with 102,141 reported cases. Deaths in the U.S. through April 26, 2021 have been estimated at 572,272[1].

From March 10 through April 24 there have been 256,342 confirmed cases of Covid-19 reported from Dallas County with 3,853 deaths, about 20% of these from long-term care facilities.[2] More than 67% percent of hospitalized cases in Dallas County have been under 65 years of age. Diabetes mellitus has been seen in about one-third of all hospitalized patients. More men than women have died, and 42% of the hospitalized cases have occurred in the Hispanic population. Specimens submitted for diagnosis of respiratory viruses in symptomatic persons show continuing positivity for SARS-CoV-2 with the latest result on 4/17/21 being 10.8%, down from an approximate peak value of 32% obtained during the first week in January 2021. Two cases of influenza in symptomatic persons were reported during the week ending July 24, 2021. Otherwise, there have been no positive tests for influenza A or B and only four tests positive for RSV in specimens from the respiratory tract from 6/6/20 through 4/24/21. Variant coronavirus cases have occurred with a total of 57 cases for B.1.1.7, 6 cases of B1.429, and 1 case for B.1.526. See article on The Variants below. Twenty-five active LTCF outbreaks resulting in cases in residents and healthcare workers are being reported. There are 9 active outbreaks in congregate living facilities (homeless shelters, group homes and halfway houses).

References:

1. Covid-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) (Updated 4/26/21)
2. Dallas County Health and Human Services. Acute Communicable Disease Epidemiology Division Updated 4/24/21

Virology Update

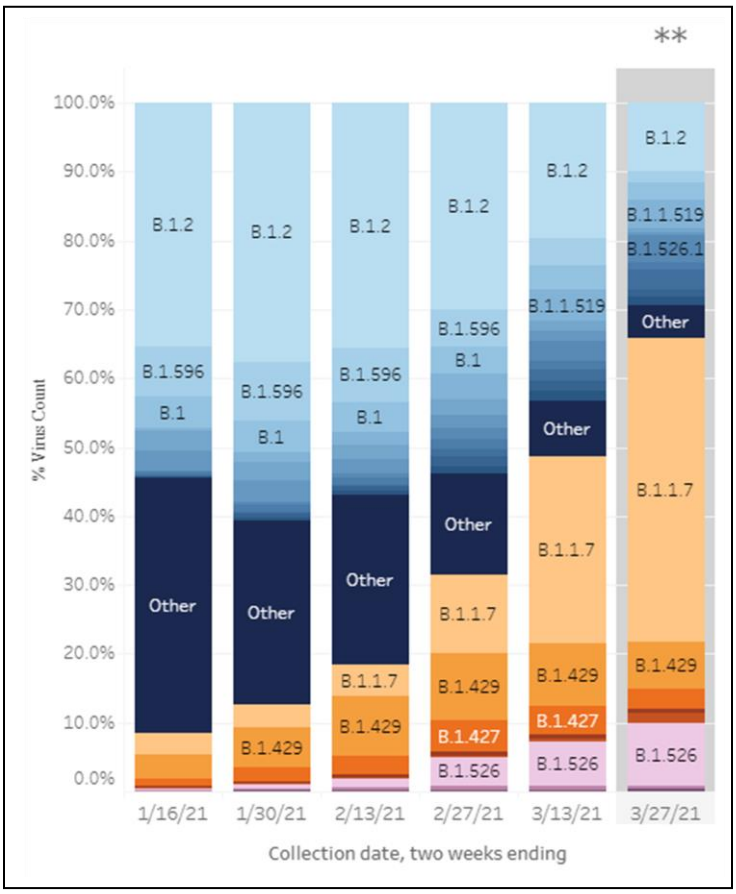
Covid-19: The Variants.
U.K. Variant B.1.1.7 Accounts for >40% of Present U.S. Cases

SARS-CoV-2 was first isolated in Wuhan, China, in December 2019. It is estimated that mutations in the virus have resulted in a change of two amino acids per genome per month. Under these conditions of continuous mutation, viruses with different genetic sequences are constantly being produced. The number of mutations and their locations in the genome determine differences in the phenotype and behavior of the resulting virus strains. For example, a prominent change involving replacement of aspartic acid (D) by glycine (G) at position 614 in the SARS-CoV-2 spike protein is termed D614G.[1] It is particularly important because it appears to be

associated with a viral phenotype that is more rapidly transmitted. It has been found in 4 of the 5 variants presently classified as "variants of concern" (see below).

Genome sequences with similar changes and sharing common epidemiologic and biological events are grouped into lineages, which are composed of a founding variant and its descendants. Lineages that persist and are transmitted between persons are known as strains or variants.

Presently, the body of SARS-CoV-2 virus lineages circulating in the U.S. have been classified by widespread, rapid sequencing into well over 200 variants, which vary widely in prevalence and behavior.[2] These are shown in the figure. Note the rapid increase in the percentage of isolates classified as B.1.1.7. This classification has been developed in the past several months by the NS3 (National SARS-CoV-2 Strain Surveillance) program involving high volume sequencing by a network of commercial laboratories contracted by CDC in partnership with the Association of Public Health Laboratories.[2]



SARS-CoV-2 variants circulating in the U.S., Jan 2020 – Mar 2021.[2]

On the basis of epidemiologic and clinical tracking, prominent lineages have been classified into three categories: variants of interest (VOI), variants of concern (VOC) and variants of high consequence (VOHC). The classification is based on changes in receptor binding, degree of neutralization by convalescent sera, transmissibility, diagnostic impact, disease severity and level of treatment efficacy.[2,3] VOC implies lineages of virus or strains that have been shown to have increased transmissibility, reduced neutralization by convalescent and post-vaccination sera, or increased clinical severity.

Of the 20 most common lineages circulating in the U.S., three have been classified as VOI, 5 as VOC and none as VOHC.[2] The 5 VOC variants with their country of origin and their prevalence in the U.S. are:

B.1.1.7 (United Kingdom, 44.1%).
B.1.429 (California, 6.9%)
B.1.427 (California, 2.9%)
P.1 (Japan, Brazil, 1.4%)
B.1.351 (South Africa, 0.7%)

Particular attention must be directed against B.1.1.7, B.1.351 and P.1 because of their potential for more rapid spread and possibly increased clinical severity.[4,5] First detected in the United Kingdom, B.1.1.7 contains mutations D614G, N501Y, P681H and a deletion at 69/70. It has been characterized in several studies by an increased rate of transmission. Initial reports suggested an increase in clinical severity, but this has not been substantiated by later reports; research to clarify this is ongoing. Convalescent sera from patients infected with this variant neutralize B.1.1.7 virus and an original reference virus containing the D641G mutation.

Originally detected in South Africa, B.1.351 is a highly transmissible virus but probably does not cause more severe disease than the prototype SARS-CoV-2 coronavirus. At nine months after clinical disease, sera from convalescent B.1.351 patients had limited neutralizing capacity against SARS-CoV-2. Three weeks after immunization with Pfizer vaccine, there was neutralization activity against prototypical SARS-CoV-2 but limited against B1.351 as demonstrated by a non-peer reviewed Israeli study in which clinical cases of B1.351 disease occurred with greater frequency than those caused by the original virus strain.

The P.1 variant was first detected in Japan among travelers from Brazil and is the primary virus stain presently producing disease in Brazil. This variant is estimated to be 2.5 times more contagious than the original strain isolated in China. Antibodies to P.1 may have only limited capacity to neutralize original strains producing Covid-19.

There are two virus variants, B.1.427 and B.1.429, now circulating in California and the U.S. Their transmissibility appears to be increased about 20%. There is only limited information on their long-term consequences, but they represent potential problems because they are not neutralized well by post-immunization antisera or by therapeutic monoclonal antibody preparations.

Summary of epidemiologic and clinical features of the 5 "variants of concern" in the U.S.						
Variant	Likely country of origin	Prevalence in U.S. (%)	Increased transmissibility	Clinical virulence	Evidence of reduced susceptibility of variant to neutralizing antibody from infection with original SARS-CoV-2 virus	Definitive evidence of increasing rate of serious breakthrough infections after complete vaccination
B.1.1.7	U.K.	44.1	Yes	Evidence conflicting	No	No
B.1.429	U.S.	6.9	Slightly (20%)	Unknown	Yes	No
B.1.427	U.S.	2.9	Slightly (20%)	Unknown	Yes	No
P.1	Japan, Brazil	1.4	Yes (2.5 fold)	Unknown	Yes	No
B.1.351	South Africa	0.7	Yes	Not increased	Yes	No

While evidence of reduced susceptibility of a mutant strain to convalescent or post-vaccination neutralizing antibody suggests the possible acquisition of the ability to spread and cause disease in a vaccinated population, there are several reasons that this may not happen.[4] Lower levels of effectiveness of neutralizing antibodies might still effectively block infection. Even if the virus becomes able to circumvent neutralizing antibody, T cell response might still provide sufficient immunity. A mutation that increases resistance to neutralizing antibody might simultaneously alter another trait important for infection, such as binding affinity for the ACE2 receptor. The reliability of studies on binding by neutralizing antibody may be reduced by the small number of sera from immunized individuals studied.

Thus, concluding that a new variant can evade vaccination is a complex decision, ultimately requiring epidemiologic evidence of an increase in the rate of serious breakthrough infections, which so far has not been definitively shown with any of the prevalent SARS-CoV-2 variants.[6] Surveillance is underway to detect such a change; the major pharmaceutical companies are actively preparing to produce new booster vaccines; and public health agencies are developing contingency plans for further population vaccination campaigns, if needed.

References:

1. Hou YJ, Chiba S, Halfman P et al. SARS-CoV-2 D614G variant exhibits efficient replication ex vivo and transmission in vivo. *Science* 2020 (Dec); 370, 1464-1468.
2. CDC Data Tracker. Variant Proportions: Estimates of SARS-CoV-2 prevalence. March 31, 2021. https://covid.cdc.gov/covid-data-tracker/#variant-proportions.
3. Planas D, Bruel T, Grzelak L et al. Sensitivity of infectious SARS-CoV-2 B.1.1.7 and B.1.351 variants to neutralizing antibodies. *Nat Med* https://doi.org/10.1038/s41591-021-01318-5.
4. Lauring AS, Hodcroft EB. Genetic Variants of SARS-CoV-2-What do they mean. *JAMA* 2021 (Feb); 325 (6): 529-531.
5. Grubaugh ND, Petrone ME, Holmes EC. We shouldn't worry when a virus mutates during disease outbreaks. *Nat Microbiol* 2020 (Mar); 5:529-530. https://doi.org/10.1038/s41564-020-0690-4.
6. Rubin R. COVID-19 vaccines vs variants—determining how much immunity is enough. JAMA 2021 (Mar); 325(13): 1241-1243. doi:10.1001/jama.2021.3370

Clinical Advance

Cerebral Sinus Thrombosis with Thrombocytopenia after J&J Janssen Vaccine

Last Friday, April 23, CDC's Advisory Committee on Immunization Practices (ACIP) met following an 11-day suspension of administration of the Johnson & Johnson/Janssen vaccine. The stated purposes of the pause were to assess the reported occurrence of 6 reported U.S. cases of cerebral venous sinus thrombosis with thrombocytopenia, officially termed **Thrombosis with Thrombocytopenia Syndrome (TTS)**, following receipt of the Janssen vaccine and to allow time to prepare the medical community to detect and treat it. Over the 11 days of the suspension, 9 additional U.S. cases were confirmed, making 15 cases in all. Based on the evidence presented,[1] the ACIP recommended resumption of the vaccine's use because the magnitude of its advantages and benefits strongly outweigh the detriment from this rare complication. Following the ACIP meeting, the CDC Director announced the end of the suspension. (Note that the European Medicines Agency found a similar link to TTS occurring after receipt of the AstraZeneca vaccine, which is not being distributed in the U.S. Both the Janssen and AstraZeneca vaccines deliver the vaccine via a non-replicating adenovirus vector, not used by the Pfizer or Moderna mRNA vaccines, which have not been reported to lead to TTS.)

Before the Covid-19 pandemic, cerebral venous thrombosis (CVT) occurred rarely at an estimated rate of 0.22-1.57 cases per 100,000 population, constituting 0.5-1% of all strokes. Women were involved 3:1 over men, with a median age of 37 years. Risk factors have included prothrombotic conditions (genetic and acquired), oral contraceptives, pregnancy and the post-partum period, malignancy, infection and mechanical precipitants such as lumbar puncture.

Characteristic presenting signs and symptoms include isolated intracranial hypertension syndrome (headache with or without vomiting, papilledema and visual problems), focal syndrome (focal deficits, seizures or both), or encephalopathy (multifocal signs, mental status changes, stupor or coma). Rare presentations include cavernous sinus syndrome, subarachnoid hemorrhage, and cranial nerve palsies.

Reported cases of CVT following the Janssen Covid-19 vaccination in the U.S. included 19 cases, of which 15 also had thrombocytopenia (<150,000/mm^3), which satisfied the case definition of TTS. (The 4 cases of CVT with normal platelet counts were considered part of the expected background rate. The Moderna vaccine was followed by 3 cases of CVT in 84.7 million doses, but all 3 had normal platelet counts; their onsets were on days 2, 6, and 12 days post vaccination. No cases of CVT followed the Pfizer vaccine.)

All 15 TTS cases were diagnosed in women. Thus, in the 3.99 million Janssen vaccine doses administered to women, the incidence rate of TTS was 3.76 TTS cases per 1 million women. The median age of the 15 cases was 37 years (age range 18-59); the distribution and incidence rate by age are shown in the **table**. The median time to symptom onset was 8 days (range 6-15 days).

Age distribution of TTS in 15 U.S. women following Janssen vaccination

Age group	TTS cases	Doses administered	Rate per million
18-29	3	579,709	5.2
29-39	7	594,215	11.8
40-49	3	692,370	4.3
50-64	2	1,367,529	1.5
≥65	0	757,710	0

Possibly predisposing factors included current estrogen/ progesterone use (n=2), and pre-existing conditions included obesity (n=7), hypothyroidism (n=2), hypertension (n=2), and asthma (n=1). None was pregnant or post-partum, and none had known coagulation disorders or diabetes.

Presenting symptoms were headache, fever, chills, back pain, myalgias, dyspnea, vomiting and malaise/lethargy. Late symptoms included severe headache (some with neck pain or stiffness), severe abdominal pain, nausea/vomiting, unilateral weakness, aphasia, gaze deviation, unilateral neglect, unilateral leg swelling, and abdominal pain, each of these in one patient.

CT scans revealed thrombosis in various cerebral sinuses (**Figures 1 and 2**, next page), accompanied in some cases by thrombosis at other sites including lower extremity veins, portal vein, hepatic vein, superior mesenteric artery, splenic artery, pulmonary artery, internal jugular vein, carotid artery, brachial vein, femoral vein and artery, and iliac artery.

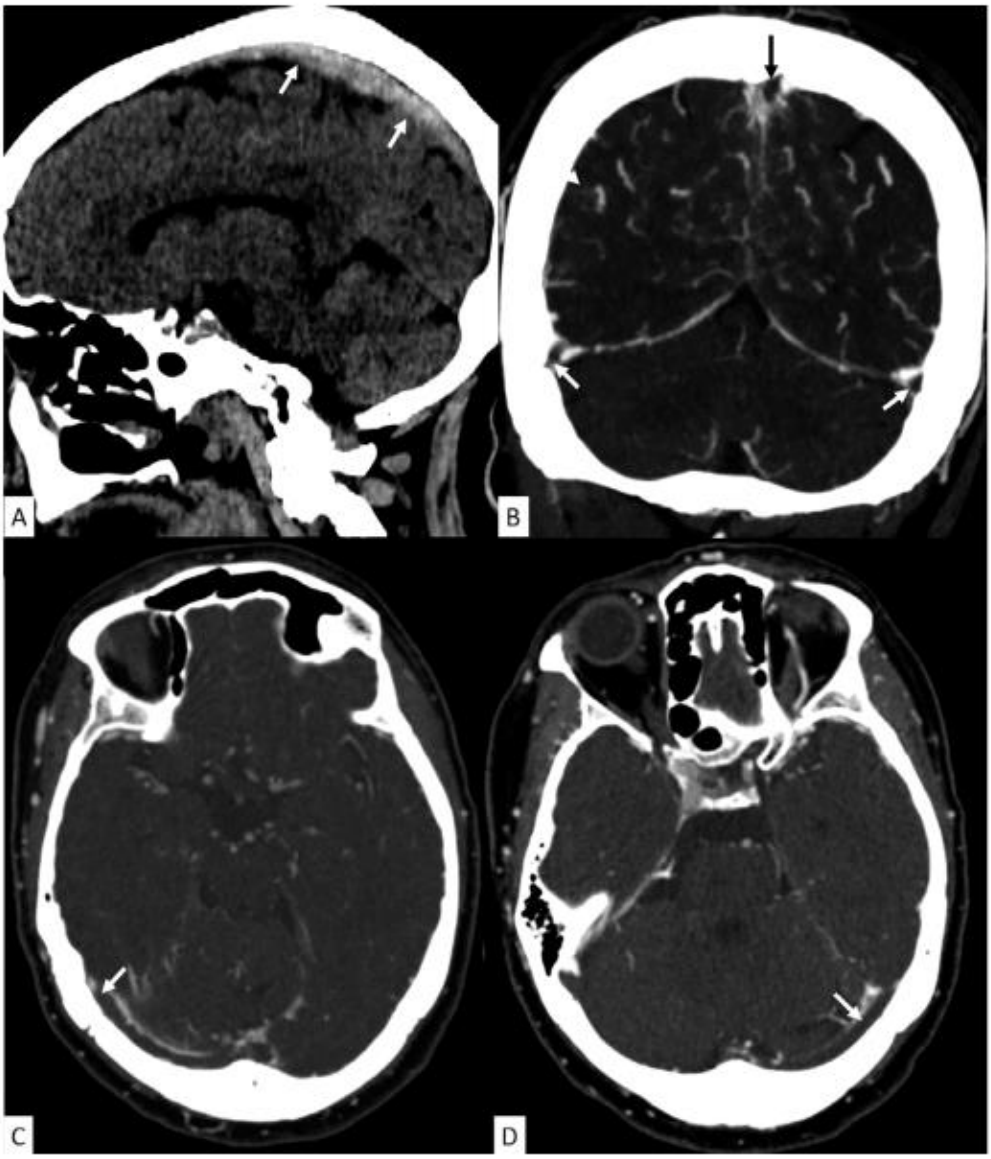


Figure 1. *A 68-year-old woman presented with fever, cough, and shortness of breath. A nasopharyngeal swab RT-PCR test resulted positive for SARS-CoV-2. Three weeks later, she returned with generalized weakness, headache, nausea and vomiting. Sagittal CT brain without contrast (A) showing abnormally dense superior sagittal sinus (white arrows). Coronal (B) and axial (C, D) CT venogram showing filling defects within the superior sagittal sinus (black arrow. B) and the bilateral transverse sinuses (white arrows, A, B and C) consistent with venous thrombosis.*
From Abdalkader et al. *J Stroke Cerebrovasc Dis* 2021; 30 (6, June): 105733

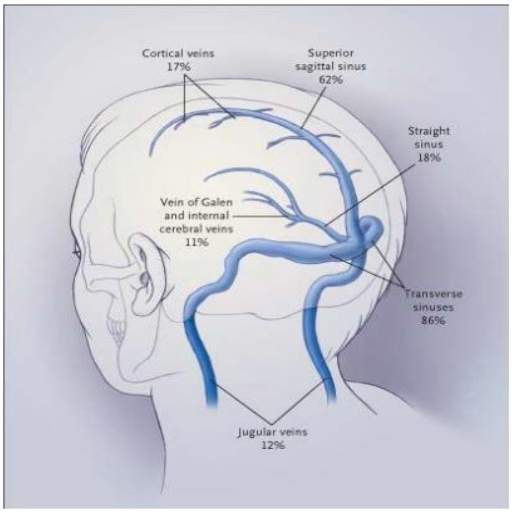


Figure 2. The main cerebral venous sinuses, from *NEJM* 2005;243:1791.

Platelet counts ranged from 10,000 to 127,000, with 10 of 15 being under 50,000. **PF4 HIT antibody, also found in the heparin-induced thrombocytopenia (HIT) syndrome, was positive in 11, negative in 0, and not available in 4.** All SARS-CoV-2 viral tests and antibody tests done were negative.

Treatments included heparin (n=6), non-heparin anticoagulants (n=12), platelet transfusion (n=7), and intravenous immunoglobulin (n=8). Three patients died, 7 remained in hospital (4 in ICU), and 5 had been discharged home.

Incidence of Cerebral Sinus Thrombosis after Janssen Vaccination vs Covid-19 Infection

The incidence of TTS after Janssen vaccination of 3.76 per million appears far lower than the best estimate of the risk of CVT within 2 weeks after a diagnosis of Covid-19 illness, reported in a recent unpublished report from Taquet et al.[2] From diagnosis codes in over 537,913 individuals with Covid-19, identified among 8 million enrolled in health plans of 59 healthcare organizations in the U.S., they estimated the rate of CVT at 43 CVT cases per 1 million Covid-19 cases in the first 2 weeks after diagnosis of the Covid-19 infection. Since the methods of case ascertainment were different in the 2 studies, the relative risk of >10 may be an overestimate, but eventual studies with comparable measurements are likely to show that the benefits of the Janssen vaccine in avoiding Covid-19 illness and its complications far outweigh its very small risks.

Take-Home Lessons for Clinicians[1]

- Maintain a high index of suspicion for women 18-50 presenting with severe headache, backache, abdominal pain, new neurologic signs or symptoms, unilateral leg swelling, shortness of breath, petechiae, or new easy bruising starting within 1-2 weeks of receiving the J&J Janssen or AstraZeneca vaccines.
- In such patients evaluate for thrombotic or thromboembolic events and test for thrombocytopenia and, if platelet count is low, test for PF4 HIT autoimmune antibody.
- Treat thrombotic events and thrombocytopenia with non-heparin anticoagulants and high-dose intravenous immune globulin. **Do not use heparin unless the HIT antibody test is negative.**
- Consult a hematologist.
- Report the case to CDC's VAERS program as required under the Emergency Use Authorizations for Covid-19 vaccines. Go to vaers.hhs.gov or call 1-800-822-7967.

References:

1. Shimabukuro T. Thrombosis with thrombocytopenia syndrome (TTS) following Janssen COVID-19 vaccine. Presentation to the Advisory Committee on Immunization Practices (ACIP), April 23, 2021.
2. Paquet M, Husain M, Geddes JR, et al. Cerebral venous thrombosis and portal vein thrombosis: a retrospective cohort study of 537,913 COVID-19 cases. Posted at OSFHOME on April 14, 2021. https://osf.io/a9jdq/

From the Editors

The aim of this periodic newsletter is to serve as a source of information for the UT Southwestern community which can lead to better understanding and control of a new disease (COVID-19) caused by the pandemic spread of an emerging viral pathogen (SARS-CoV-2). We welcome questions, comments, and suggestions for topics and authors.